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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,795	09/05/2001	Gunther Berndl	49727	4232

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EXAMINER	
GOLLAMUDI, SHARMILA S	
ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,795	BERNDL ET AL.	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Request for Continued Examination received December 4, 2003, Amendments/ Remarks received on March 5, 2004, and the Information Disclosure Statement received on November 26, 2003 is acknowledged. Claims **1-6** are pending in this application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baert et al (6,365,188) in view of Nagafuzi et al (5,290,569).

Baert et al teach a solid mixture of cyclodextrin prepared via melt extrusion. The melt-extrusion mixture contains cyclodextrin and an active agent. See column 3, lines 26-40. Baert discloses that cyclodextrins increase the solubility of the insoluble drugs such as anti-fungals. Any suitable compound may be utilized provided that the drug does not decompose at high temperatures. See column 2, lines 45-60. Baert teaches melt-extrusion as the polymer extrusion

technique wherein an active agent is embedded in one or more carriers. In this technique the active and excipients are molten in the extruder and hence embedded in the thermoplastic and thermomelting polymers. See column 3, lines 26-40. Additionally, the mixture may contain additives such as instant polyethylene glycol. See column 4, lines 34-42. The process includes a) mixing the cyclodextrin with the active agent and additives, b) heating the mixture until melting of one of the components occurs, c) forcing the mixture through one or more nozzles, and d) cooling the mixture to obtain a solid product. See column 4, lines 15-25. Although, a temperature of 239 degrees Celsius is exemplified, Baert discloses that different temperatures may be applied and discloses the method of ascertaining the required temperature. See column 5, lines 1-12. The extruder has counterotating screw with different shapes. See column 5. The melt-extruded mixture is preferably prepared without water or a solvent. The preferred ratio of the active to cyclodextrin is 1:3. See column 7, lines 64 to column 8, lines 4 and examples.

Baert et al do not teach the instant amount of the polymer in the extrusion mixture or the molecular weight of the PEG. Additionally, Baert does not teach the instant temperature of 220 degrees Celsius.

Nagafuzi et al teach a process for preparing a coated composition containing an active agent that is stable to heat and a thermomelting material under heating and coating the resulting granules with a second thermomelting material. See abstract. Nagafuzi teaches the first thermomelting material as one that melts readily at 50 to 150 degrees Celsius to provide a low viscous material. Typical examples of thermomelting material are polyethylene glycol with an average molecular weight preferably between 2000-20,000. See column 2, lines 14-35. The thermomelting material is utilized in an amount of 0.05-0.4 parts by weight to one part by weight

of active agent. See column 3, lines 35-40. Nagafuzi et al teach the amount of both cyclodextrin and active in instant amount (Example 1). The reference teaches the process of heating the composition below 220 degrees Celsius without a solvent (col. 1, lines 49-55).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Baert et al and Nagafuzi et al and incorporate PEG with the instant molecular weight into Baert's process. One would be motivated to do so since Nagafuzi teaches that the instant polyethylene glycol polymer is a typical thermomelting material are pharmaceutically acceptable and conventionally utilized in extrusion processes to yield a low viscous composition.

Further, Nagafuzi teaches the PEG melts readily at 50-150 degrees Celsius, which meets instantly claimed temperature since Baert states that the extrudate is heated until the "melting of one of the components".

Lastly, Nagafuzi teaches the amount of thermomelting material, i.e. PEG, is utilized in the amount of 0.05-0.4 parts by weight to one part by weight of the active agent, thus the instant concentrations would fall within instant scope depending on the amount of active agent utilized.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mueller et al (5,552,159) in view of Baert et al (6,365,188).

Mueller teaches a solid depot drug form produced by melt extrusion at a temperature from 50 degrees to 200 degrees Celsius. The extrusion composition contains a pharmaceutically active ingredient in the amount of 0.1-70% and a polymer melt composition of a) at least 6% of a water insoluble poly(meth) acrylate, b) a water-soluble hydroxyalkylcellulose or an N-vinylpyrollidone polymer with 0-50% vinyl acetate, and c) 0-30% of a conventional additives.

See abstract. The ratio of the polymer a to polymer b is 5:95 to 95:5. se column 2, lines 60-65. The pharmaceutical agent is any substance with pharmaceutical action and does not decompose under processing conditions. See column 2, lines 17-25. The process is a simple and environmentally acceptable since it does not require a solvent in the process. See column 3, lines 52-53. The shaping of the extrudate is effected by passing the extrudate between two counter-rotating rolls with opposite depression on their surfaces. See column 3, lines 23-30. The tablet may be coated after the shaping process. See column 3, lines 45-20. Mueller states that the extrudate composition is superior to other simple extrusion methods since the at least one water-insoluble polymer and at least one water-soluble polymer provide stability from mechanical stress.

Mueller does not teach the use of a cyclodextrin and active agent combination.

Baert et al teach a solid mixture of cyclodextrin prepared via melt extrusion. The melt-extrusion mixture contains cyclodextrin and an active agent. See column 3, lines 26-40. Baert discloses that cyclodextrins increase the solubility of the insoluble drugs such as anti-fungals. Any suitable compound may be utilized provided that the drug does not decompose at high temperatures. See column 2, lines 45-60. Baert teaches melt-extrusion as the polymer extrusion technique wherein an active agent is embedded in one or more carriers. In this technique the active and excipients are molten in the extruder and hence embedded in the thermoplastic and thermomelting polymers. See column 3, lines 26-40. Additionally, the mixture may contain additives such as instant polyethylene glycol. See column 4, lines 34-42. The process includes a) mixing the cyclodextrin with the active agent and additives, b) heating the mixture until melting of one of the components occurs, c) forcing the mixture through one or more nozzles, and d)

cooling the mixture to obtain a solid product. See column 4, lines 15-25. Although, a temperature of 239 degrees Celsius is exemplified, Baert discloses that different temperatures may be applied and discloses the method of ascertaining the required temperature. See column 5, lines 1-12. The extruder has counterotating screw with different shapes. See column 5. The melt-extruded mixture is preferably prepared without water or a solvent. The preferred ratio of the active to cyclodextrin is 1:3. See column 7, lines 64 to column 8, lines 4 and examples.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Mueller and Baert et al and utilize the instant cylcodextrin and active agent combination. One would be motivated to do so since Baert teaches the cyclodextrin and active agent combination provides for increased solubility of the active agent in the dosage form. Further, Baert states that the antifungal and cyclodextrin are capable of withstanding high temperatures of the melt-extrusion process.

Conversely, it would have been obvious for one of ordinary skill in the art at the time the invention was made to look to Mueller and incorporate his teachings into Baert et al. One would be motivated to do so since Mueller teaches a stable extrudable composition that is manufactured in a similar process seen in Baert et al. Mueller teaches the polymer composition is stable because it withstands mechanical stress compared to other similar extrudable compositions. Therefore, one would be motivated to add the polymer carriers taught in Mueller et al to increase the stability of Baert's extrudable composition. Additionally, one would expect similar results since Baert teaches additional thermomelting additives and states that in melt-extrusion techniques the active can have one or more carriers.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/58529 to Meerpoel et al in view of Klimesch et al (4,880,585).

Meerpoel teaches a water-soluble azole as broad-spectrum antifungals. The composition may be in the form of an oral or rectal composition obtained by melt-extruding mixtures of the inventive compound and one or more pharmaceutically acceptable water-soluble polymers. The technique comprises the following steps: a) mixing the active and appropriate water-soluble polymers, b) optionally mixing blending additives, c) heating the obtained blend until a homogenous melt is formed, d) forcing the melt through one or more nozzles, and e) cooling the melt until it solidifies. See page 27. Suitable water-soluble polymers taught are cellulose derivatives, starches, polysaccharides, polyvinylpyrrolidone, copolymers of PVP with vinyl acetate, , etc. See page 28. Further, instant cyclodextrins are also taught as suitable water-soluble polymers. The ratio of the active to cyclodextrin is in the ratio of 1/5 to 5/1; however it can vary. See page 28.

Meerpoel does not specify the melting temperature or the amount of the water-soluble polymers. Additionally, the reference does not teach the use of molding calendars.

Klimesch et al teaches a method of continuous tableting using a molding calendar with opposite rollers (col. 1, lines 16-27). The reference teaches the use of instant polymeric binder (PVP and copolymers of PVP) and instant temperature (col. 2, lines 40-68). The reference teaches the preferable temperature is 60-130 degrees Celsius to be extrudable and the temperature may be reduced by utilizing a plasticizer. See column 3, lines 1-10. Klimesch teaches that the instant polymer is is conventional and convert the pharmacological actives into paste to be extruded. The advantage of the process is it makes premixing unnecessary (col. 1,

lines 28-34). The active agent may be incorporated in the amount of 01-95 and in particular from 30-70%. See column 4, lines 29-40. Various ratios of the active/polymer/auxiliary are taught in Table 1. For instance, the active may be in the amount of 50% and the polymer may be in the amount of 50%. See example 32. In particular, the composition contains an active and 30-100% of a NVP polymer. See claim 1.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Meerpoel et al and Klimesch et al and incorporate Klimesch's teachings into Meerpoel's. One would be motivated to do so since Klimesch teaches that the water-soluble polymers taught in Meerpoel, i.e. PVP and PVP copolymers with vinyl acetate, are conventionally utilized in extrusion processes to make the composition into a paste and melt in the range of 60-130 degrees; thus meeting instant temperature limitation.

Further, Klimesch teaches various ratios of the active ingredient and polymer, optionally containing an additive. The manipulation of the active, polymer, and various additives is deemed to be obvious to one of ordinary skill in the art by following the guidance provided by the prior art.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sharmila S. Gollamudi
Examiner
Art Unit 1616

SSG

MICHAEL G. HARTLEY
PRIMARY EXAMINER